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Saving Time in Blood Culture Diagnostics: a Prospective Evaluation of the Qvella FAST-PBC Prep Application on the Fast System

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ABSTRACT Time to results for identification (ID) and antimicrobial susceptibility testing (AST) from blood cultures is an important factor impacting outcome in sepsis. In this study we evaluated a novel device, the FAST™ system from Qvella that concentrates microbial biomass from positive blood culture flasks with the FAST-PBC Prep™ cartridge thereby producing a liquid colony™ (LC), which can be used immediately in standard laboratory downstream applications. We tested 250 positive blood culture bottles collected from January 2021 to May 2021. Results were obtained either with LC or from bacterial overnight cultures using Bruker's MALDI Biotyper™ and bioMérieux's Vitek 2. We compared ID and AST results obtained by both methods and evaluated turnaround times. Two-hundred and fourteen blood cultures could be included in the analysis. In 94% of the cases (n = 201) identification was obtained directly from the LC with concordant results compared to the standard workflow. No discordant results were observed. AST results could be analyzed for 175 samples. Using categorical analysis, concordant agreement was 97.4% of 1,676 AST results for Gram positive bacteria. Agreement for Gram negative bacteria was 98.5% of 980 AST results. Times-to-result were 36.9 h versus 12.8 h for ID and 52.9 h versus 26.8 h for AST in routine workflow vs FAST™ system, respectively. The FAST™ system gives reliable results for ID and AST directly from positive blood cultures and allows for significant time savings in blood culture diagnostics.

KEYWORDS blood culture, diagnostics

Despite recent improvements, bloodstream infections continue to result in high mortality rates and significant financial burden to health care providers (1–3). It has been shown that time until initiation of empirical antibiotic treatment impacts patient outcomes (4, 5). Moreover, it has also been suggested that decreasing the time until targeted and effective therapy can be initiated, e.g., by employing rapid methods for identification (ID) and antimicrobial susceptibility testing (AST), might help to reduce patient mortality, length of hospital stay and costs for the health care provider (6–8). Because of the increasing rates of resistant bacteria, early identification and antimicrobial susceptibility testing of bacteria causing bloodstream infections is an important aim that so far is only partly achieved by routine microbial procedures. Furthermore, inappropriate early antibiotic therapy may also lead to prolonged hospital stays with increased mortality and morbidity (9–12). In addition, prolonged inappropriate treatment increases risks of infection with multidrug-resistant bacteria (12, 13).

Diagnosis of bloodstream infections from positively flagged blood culture bottles requires considerable time until final identification and antimicrobial susceptibility testing results are available. Laboratories that use overnight subculturing to grow microbial colonies for pathogen identification and AST usually have a turnaround time of 2 to 3 days (14). Internal laboratory workflows (e.g., workshifts) may delay the diagnostic

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process further. Although more rapid workflow and techniques have become available, many of those either require significant changes in the laboratory workflow or are still in the developmental stage. Efforts have been made to develop methods that can help to reduce turnaround times. Among these are various new devices, changed protocols or specially developed kits for sample enrichment and preparation directly from positive blood culture (15–20). This study aimed to investigate a new system, the FAST™ system (Qvella, ON, Canada). The FAST™ system concentrates biomass from a 2 mL aliquot of positive blood culture bottles using specific cartridges that require minimal hands-on time. After 30 to 40 min, a LC is obtained that should be compatible with common downstream applications for organism ID and AST. In the present study we set out to compare the FAST™ system workflow with a routine analysis of overnight subculture. IDs were obtained via Bruker's MALDI TOF and ASTs with bioMérieux's VITEK2.

MATERIALS AND METHODS

Study samples. Two-hundred and fifty blood culture bottles (BD Bactec™ plus Aerobic, BD Bactec™ Lytic Anaerobic or BD Bactec™ Peds Plus™, BD, Heidelberg, Germany) flagging positive for growth of microbes were used. Blood cultures had been drawn under hospital standard conditions and were collected from January 2021 to May 2021 at a single center, tertiary care hospital Carl Gustav Carus in Dresden, Germany. Any true blood culture flask was eligible except for the following exclusion criteria: processing >16 h after flagging positive, blood cultures from patients that had already been included in the study probably uneccessary, and postmortem blood cultures. From every set of blood culture bottles, only one was included in the study. Incubation was done in the Bactec™ FX. Polymicrobial blood cultures, that were identified either by Gram staining or via an overnight purity plate, were excluded from the study. Use of anonymized samples was approved by the local ethic committee (BO-EK-291072020).

Routine workflow. The regular workflow included streaking and overnight subcultivation on Columbia 5% sheep blood agar plates (Thermo Scientific™ Oxoid™) followed by identification via MALDI TOF and AST via VITEK2. Discrepancy analysis was performed using the gradient diffusion test (Liofilchem srl, Roseto degli Abruzzi, Italy) on Muller-Hinton-Agar (Mueller-Hinton E Agar, bioMérieux).

FAST™ system. The FAST™ system (Qvella, ON, Canada) was used with positive blood cultures according to the instructions by the manufacturer. Briefly, 2 mL of a recently positively flagged blood culture (<16 h after becoming positive) was pipetted into the single-use FAST-PBC Prep™ cartridge of the system and processed in the FAST™ instrument. By separating blood components from bacteria, a liquid colony™ (LC) of 80 to 100 μL is produced which is a suspension of viable pathogens. The blood culture sample undergoes a process of controlled digestion of the blood cells and centrifugal separation of these components from the target microorganisms. The process is automated and requires less than 2 min of hands-on time. The automated procedures then take 30 to 40 min. The liquid colony obtained was then used for downstream processing using the same methods as in the routine workflow described above.

Identification. MALDI Biotyper -MBT Smart (Bruker Daltonik, Bremen, Germany) and MBT Compass IVD 4.2. were used for identification. All measurements from liquid colony were performed on a polished steel reusable MALDI target with the addition of formic acid (70%). Routine measurements were done on disposable MALDI targets (MBT Biotargets 96) without the addition of formic acid. IVD bacterial test standard (BTS) as well as IVD HCCA Matrix were both acquired from Bruker and mixed with standard organic solvent according to the manufacturer's instructions. ID measurements from LC were always done in duplicate. If the initial measurement failed, a second measurement of the same sample was performed. According to the internal and approved routine workflow, correct identification was assumed when a MALDI score was >=2.0, or for scores >1.7 but <2.0 when the first, second, and third best match were giving the same species (based on data by Klein [21] and Schubert [15]).

Antimicrobial susceptibility testing. For AST bioMérieux Vitek 2 (bioMérieux, Lyon, France) system was used together with the Advanced Expert System™-software version 9.02 and the appropriate Vitek AST cards. Standard inoculum was prepared either from overnight subculture or from LC and adjusted to McFarland 0.5 (0.49 to 0.63 acceptable). Whenever an AST was performed, a purity control plate on Columbia 5% blood agar was also prepared from the inoculum and incubated overnight. Initial discrepancies after AST from both study arms were analyzed by repetition via the gradient diffusion test.

Time to results. We measured the time to ID and to AST within the routine diagnostic workflow starting from the time point when the Bactec™ FX gave a positive signal. MALDI ID and AST preparation were done in the routine workshift from 7 a.m. to 4 p.m. According to the manufacturer's recommendations and considering the on-site working hours, blood cultures with >16 h after positivity were not analyzed. For both workflows average times were calculated and compared.

RESULTS

Study samples. Out of 250 initial patient blood culture bottles, 36 (14%) were excluded: Of those, 35 were polymicrobial samples and one did not produce any growth on agar plates in both workflows. The remaining 214 mono-microbial blood cultures

TABLE 1 Identification by FAST™ system workflow[a]

Correct identification	"No ID from LC" (MALDI score <1.7)	"No peaks from LC"
201 (94%)	7 (3%)	6 (3%)
	Gordonia bronchialis	*Bacillus cereus*
	Kocuria rhizophilia	*Candida albicans*
	Leptotrichia trevisanii	*Cryptococcus neoformans*
	Proteus mirabilis	*Enterobacter cloacae comp.*
	Staphylococcus epidermidis	*Pseudomonas aeruginosa*
	Staphylococcus saccharolyticus	*Staphylococcus hominis*
	Streptococcus sanguinis	

[a]MALDI results separated into correct ID (94%) and unsuccessful ID (6%). Also shown are species ID for unsuccessful cases obtained from routine workflow. LC, liquid colony.

were included for further analysis. Gram staining was performed before further downstream processing. We processed 134 (62.6%) blood cultures with Gram positive pathogens (3 proved to be yeasts) and 80 (37.4%) containing Gram negative bacteria.

Use of the FAST™ system. Technically, we observed 18 failed runs in total with the FAST™ system during the study period. Of those, nine cartridge processing errors with failures in separating bacteria from blood components were encountered, the other nine failures were software or hardware related. Each failed run was repeated once, thereafter we obtained from all of them a LC. If repetition was required, the additional time of roughly 40 min was considered in the time-to-result analysis.

Identification results. Throughout the study we encountered 33 different microbial species (Table S1). The most common bacteria encountered were *Escherichia coli* ($n = 33$) and *Klebsiella pneumonia* ($n = 12$) for Gram negative bacteria, and *Staphylococcus epidermidis* ($n = 38$) and *Staphylococcus aureus* ($n = 23$) for Gram positive bacteria. Of all MALDI tests performed from the LC, 201 out of 214 (94%) gave a successful identification. Thirteen samples were successfully identified by the routine workflow but gave no result when the LC was used (6%). For the 201 successful results from the LC, all yielded concordant results with routine ID (Table 1). There were no discordant ID results between the routine and the FAST™ system workflow throughout this study whenever the LC gave a successful result. The remaining 13 samples did not yield acceptable results by MALDI for the LC. These 13 samples either had scores below 1.7 ($n = 7/13$) or gave no peaks at all ($n = 6/13$) from the LC (Table 1). They were retested once according to the study protocol but failed to produce results on the second attempt.

Average MALDI-scores for Gram positive pathogens were 2.03 (SD $\pm$ 0.17) and 2.09 (SD $\pm$ 0.20), and for Gram negative bacteria 2.17 (SD $\pm$ 0.14) and 2.26 (SD $\pm$ 0.13) for the FAST™ system versus routine workflow, respectively. We used criteria as outlined in the Materials and Methods section for positive identification. When using a sharp score of 2.0 as cut-off, LC gave results for 75/125 versus 90/125 for routine procedure for Gram-positive bacteria, and 64/76 versus 71/76 for Gram-negative bacteria. Of note for each of the corresponding samples, LC gave the same ID, yet with a lower score.

Antimicrobial susceptibility testing results. We compared each individual drug-bacteria AST combination using a categorical analysis approach based on EUCAST 2020 breakpoint tables. First, we analyzed for absolute agreement in the susceptibility interpretation. Errors in agreement were classified as either very major errors (VME: resistant in routine versus susceptible from LC), major errors (ME: susceptible in routine versus resistant from LC), or minor errors (mE: routine or LC classified as susceptible at increased exposure [I] while the respective other workflow yielded either a susceptible or resistant result).

The results of different drug-bacteria AST combinations for all attempted and successfully completed Vitek test runs are shown in Table S2. Of the 201 initial samples with identification, 11 LC samples (5.5%) did not contain sufficient biomass to obtain the required McFarland value of 0.5 for AST. Another 10 LCs (5%) contained pathogens that are not routinely tested in the Vitek system and were tested separately using the

TABLE 2 Categorical agreements of drug-bacteria combinations between LC and routine workflow[a]

Gram stain	AST Agreement LC/Routine workflow	*N*	%
Gram pos	Categorical agreement	1,676	97.4
	VME	11	1.9
	ME	9	0.8
	mE	24	1.4
Gram neg	Categorical agreement	980	98.5
	VME	3	2.0
	ME	3	0.4
	mE	9	0.9

[a]Data calculated from initial antimicrobial susceptibility testing (AST) results, as well as number and category of errors encountered from those samples (VME, very major error; ME, major error; mE, minor error).

gradient diffusion technique. Furthermore, three runs from LC (2x *Enterococcus faecalis* and 1x *Staphylococcus epidermidis*) (1.5%) could not be completed by the Vitek system and were cancelled for unknown reasons. Finally, two samples (1%) turned out to be heteroresistant, containing a single bacterial species with different resistance profiles. Thus, 175 out of 201 (87%) ASTs from liquid colony could be evaluated in the analysis.

Categorical agreements were 97.4% and 98.5% for Gram positive and Gram negative bacteria, respectively (Table 2). For Gram positive pathogens, there were 11 VME (1.9%) and nine ME (0.8%). For Gram negative bacteria errors encountered were three VME (2.0%) and three ME (0.4%). The investigation of the 14 VME and 12 ME showed that in all but one case the initial discrepancies could be pinpointed to a measuring error in either one of the two workflows after which an agreement was achieved (Table S3). All errors with Gram positive bacteria (n = 20) were registered for coagulase-negative staphylococci (CONS). Eight out of nine major errors (89%) were resolved via gradient diffusion test and showed that the initial discrepancy in those cases occurred when testing from the LC. Of the very major errors with Gram positive bacteria (n = 11), seven were resolved via the gradient diffusion test: one discrepancy, namely, for gentamicin, was attributed to the FAST™ system workflow, while the remaining six errors were found in routine workflow. The remaining four very major errors were all found when testing teicoplanin on CONS. Retesting was performed by the disk diffusion method and the results showed no discrepancies in inhibition zone. Error analysis for Gram negative bacteria revealed that all discrepancies could be attributed to the LC workflow.

Time savings. We evaluated time savings that occurred from replacing the overnight cultivation of positive blood cultures with the FAST™ system. Due to the work-up in normal workshift hours, blood culture bottles could be processed after flagging positive on average after 7.25 h+/–3.77 h (SD) (max. 15.4 h; min. 0.2 h). For both identification and AST, usage of the liquid colony led to a considerable decrease in time-to-results by roughly 1 day. For ID, time-to-result was 12.8 h versus 36.9 h, and for AST 26.8 h versus 52.9 h for the FAST™ system versus the routine workflow, respectively.

DISCUSSION

We evaluated the FAST™ system that promises to speed-up the blood culture diagnostic workflow by preparing a "liquid colony"™ from a positive blood culture flask for immediate processing with downstream applications. In our study, we tested the FAST™ system head-to-head with a routine workflow using overnight subculture, ID by MALDI-TOF and AST with the Vitek®2 system. We found highly accurate identification directly from the liquid colony (94%). As it has been shown that MALDI scores for procedures directly done form blood cultures might be lower, we used criteria as suggested by Klein (21) and Schubert (15), outlined in the Materials and Methods section, that used a cut-off 1.7. We also found very good agreement for AST (97.4% for Gram positive bacteria and 98.5% for Gram-negative bacteria). Few very major errors were encountered. VMEs may have clinical implications as a patient might receive a drug for

a microorganism tested susceptible by LC that should have tested resistant according to the standard procedure.

The workflow itself has the intrinsic limitation of being compatible only with monobacterial cultures. We used the FAST™ system according to the manufacturer's recommendation which exclude use once a blood culture has flagged positive more than 16 h ago. We have not systematically explored the influence of time between flagging positive and removal for further processing in this study and we cannot exclude that immediate processing after flagging positive changes the results. In our study, it took on average 7.25 h before the blood culture was removed for further analysis with the FAST™ system.

This is one of the first studies evaluating the performance of this novel approach. Limited data have been presented on the FAST™ system with quite similar findings: ID concordance was equally high ranging from 87% up to 100%. Categorical agreement in AST was reported to range for both Gram positive and Gram negative bacteria from 98% up to 99.6% when compared to the respective routine methods used (22–24). A limitation of our study is the sample size of 250 blood cultures.

In addition to the evaluation of the technical performance, our data show that significant time savings can be achieved when using the FAST™ system compared with the standard workflow that relies on overnight subculture. However, it should be noted that the amount of time saved will depend on the details of integration and that there may be less time saved for blood cultures that flag positive outside of workshifts. Future studies will have to analyze how these rapid results impact clinical treatment and outcome. The FAST™ system can run a maximum of two cartridges in parallel, requiring approximately 40 min for both with little hands-on time. Based on the number of positive blood cultures in a mid-sized microbiology lab, this procedure would require either multiple devices, consecutive work-up, or restriction to certain blood cultures. Considering costs, a strategy could be to refine the use to blood cultures from ICU patients and to avoid repeat blood cultures.

Although the FAST™ approach does add additional costs, cost-effectiveness of rapid diagnostics for positive blood cultures has been reported that would compensate increased clinical laboratory costs (25).

Alternatives for rapid blood culture diagnostics are becoming more frequent. A rapid ID method is Bruker's Sepsityper Kit™ (Bruker Daltoniks, Bremen, Germany) that produces a bacterial pellet suitable for MALDI-TOF analysis (15). A meta-analysis of performance reports by Morgenthaler and Kostrzewa reported that out of 3,320 blood cultures, the Sepsityper kit allowed for reliable species ID in 80% of cases. Hands-on-time with the kit was reported to be around 30 min. The reduction of time to results was found to range from 8 h to >48 h (16). While the Sepsityper kit allows more samples to be processed in a given time frame, the steps necessary to do so are still manual and require experienced lab personnel. An advantage of the FAST™ system is that the LC cannot only be used for ID but also for AST. For another commercially available kit, the bioMérieux Vitek®MS Blood Culture kit, similar findings have been reported: Fothergill et al. investigated the ID performance of this lysis-filtration method. They reported concordant ID to the species level in 78% of blood culture bottles. To prepare three samples for identification, roughly 15 to 20 min were needed (17). Machen et al. evaluated the possibility of using the lysis-filtration method in combination with full panel AST testing methods, such as Vitek 2, to generate ID and AST results. Their findings show high agreement in ID with 94% to the species level. Categorical agreement for AST for all samples tested was 93.5% with minor errors appearing at a rate of 3.6%, major errors at 1.7%, and very major errors at 1.3%. Time to results when performing all downstream tests immediately was reported to be roughly 1 h for ID and 11.4 h for AST (18). The findings of Machen et al. come very close to those observed in our study. A further approach to speed up microbial diagnosis is the rapid AST (RAST) method from the European committee of antimicrobial susceptibility testing (EUCAST). However, RAST is only possible for certain bacteria and requires readings after 6 h or 8 h using own breakpoint tables and inhibition zone interpretations. Results showed that 8 h of incubation are enough for readable inhibition zones in 98% to 100% of isolates

while inhibition zones were readable at 6 h for 89% to 100% of isolates (20). EUCAST has performed a laboratory test run at 55 test sites across Europe to evaluate the RAST performance under everyday diagnostic conditions. Results show similar times until inhibition zones could be read at 96% and 99% after 6 h and 8 h, respectively (19). The EUCAST RAST method successfully showed that overnight subcultivation, at least for the most common bacteria in bloodstream infections, is not necessary to achieve reliable AST results. Yet, the RAST method requires considerable changes in the laboratory workflow and due to the extended incubation period, processing of positive blood culture flasks in a single workshift is challenging. Compared with the AST results obtained via LC, results from RAST are achieved faster, as the FAST™ system still relies on a downstream AST application.

To summarize, our findings show that the FAST™ system integrates well into a downstream process with Bruker's MALDI TOF and bioMérieux's Vitek®2. It delivers reliable and equally accurate ID and AST results when compared to those of a routine workflow. In addition, we observed substantial time savings of 24 h or more over bacterial subcultivation methods. The data indicate that the direct enrichment approach of the FAST™ system has the potential to improve patient outcomes due to a more rapid delivery of ID and AST results.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

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